Remarks

Claims 1-20 are pending in the present application. Claims 12-20 have been withdrawn. Claims 1-8, 10, 11 and 17 are amended herein. Claim 20 is canceled herein without prejudice, and has been filed in a divisional patent application. Claims 21-50 are added herein. Support for these amendments and new claims can be found throughout the specification and claims as originally filed. For example: claims 21-23, 29-31, and 42-44 on page 2, lines 24-30; claims 24, 32, and 45 on page 15, lines 21-29; and claims 35-36 and 48-49 on page 15, lines 9-18. No new matter is added by these amendments and new claims, and their entry and substantive examination are respectfully requested.

I. Information Disclosure Statement

Applicants have filed an Information Disclosure Statement, and a listing of references cited, concurrently with the present response. Applicants respectfully request that these references be considered by the Examiner and be made of record in the present application.

II. Claim Rejections—35 U.S.C. § 112 Indefiniteness

A. Claims 1-11 stand rejected as indefinite over the recitation of the phrase "of known polymorphisms" recited in claims 1-3, in reference to a percentage of HLA Class I polymorphisms represented by a plurality of probes. Specifically, the Office Action states that it is unclear if the polymorphisms are those known at a particular time, or available from a particular public database. In response, it is respectfully asserted that those skilled in the art can acquire various HLA Class I polymorphisms from, inter alia, the literature available at the time of the search, and the available databases. Nonetheless, Applicants have amended claims 1-3 to delete the word "known" in order to simplify the issues. Withdrawn claim 17 has also been amended for consistency.

B. Claims 1-11 stand rejected over the recitation of the term "represent" in regard to the relationship between probes on a solid support and polymorphisms in the HLA Class I locus. The Office Action states that it is "unclear what relationship between probes and polymorphisms is encompassed by this language; for example, does applicant intend some particular level of

complementarity between the required probe and a polymorphic form of an HLA Class I locus nucleic acid sequence." In response, Applicants have amended the claims to replace the phrase "being sufficient to represent" with the more common term "comprises" in order to simplify the issues. Withdrawn claim 17 has also been amended for consistency.

C. Claim 5 stands rejected as indefinite over the recitation of the phrase "has 20 nucleic acids" in reference to a plurality of HLA Class I oligonucleotide probes. The Office Action states that it is likely that Applicants had intended to recite "has 20 nucleotides." Applicants have amended claim 5 as suggested by the Examiner.

D. Claims 6-8 stand rejected as indefinite over the recitation of the phrase "said HLA Class I oligonucleotide probe." The claims have been amended to reflect the plural form of the oligonucleotide probes comprising the plurality recited in claim 1, from which claims 6-8 depend. Claims 4, 5, 10 and 11 have also been amended for consistency.

In consideration of the above-mentioned amendments and remarks, it is respectfully requested that these indefiniteness rejections of claims 1-11 be withdrawn.

III. Claim Rejections—35 U.S.C. § 102

Claims 1-3 stand rejected under 35 U.S.C. § 102(b) by U.S. Patent No. 5,474,796 to Brennan. This rejection is respectfully traversed.

Anticipation under this section requires that each and every recitation of the claim be found in a single prior art reference. *W. L. Gore & Associates Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1554, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1983). A finding of anticipation further requires that there be no difference between the claimed invention and the disclosure of the cited reference as viewed by one of ordinary skill in the art. *Scripps Clinic & Research Foundation v. Genentech Inc.*, 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991). Finally, the mere naming of a composition in a reference, without more, cannot constitute a description of the compound. *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968).

The Office Action at Page 5 claims that the microarray of Brennan "comprises every 10-

mer nucleic acid, thus it would inherently comprise a plurality of probes sufficient to represent at least 80%, 90%, and 98% of known polymophisms in the HLA Class I locus." Applicants respectfully disagree. Specifically, Applicants assert that the enormously broad genus of every possible 10mer (i.e., 4^{10}=1,048,576 individual 10mers) does not specifically or inherently name or describe any particular, individual polymorphism in the HLA Class I locus.

> There appears to be no question that the [asserted] patent does not specifically name, describe or claim any particular, individual compound anticipating [Applicants'] claims. . . . Thus, this is not a case where a reference patent imputes particular characteristics to a readily prepared, *specifically named* and *identified* compound or composition, and a party seeking to claim the *very same* compound or composition must prove that the patent description was erroneous and that what the patent at first blush appears to expressly describe never actually existed.

In re Kalm 154 U.S.P.Q. 10, 12-13 (CCPA 1967).

Because the Brennan reference fails to describe HLA Class I polymorphisms, it fails to anticipate Applicants' claims. Accordingly, it is respectfully requested that this rejection of claims 1-3 be withdrawn.

IV. Claim Rejections—35 U.S.C. § 103

A. Claims 1-8 stand rejected under 35 U.S.C. § 103(a) over Bettinotti et al. (1997) in view of European Patent No. EP0785280 to Sapolsky et al. (1997).

Bettinotti et al. describes the use of PCR amplification as a means of typing HLA-A, B, and C alleles by direct sequencing of the PCR products obtained using genomic DNA as the template (See the Title of the Bettinotti article). Applicants do not dispute that Bettinotti can be used to show that sequence information pertaining to HLA Class I alleles can be obtained from publicly-accessible databases. This is confirmed in Applicants' disclosure, e.g., on page 15, lines 20-29. However, as admitted in the Office Action on Page 7, Bettinotti does not teach a microarray comprising a plurality of HLA Class I oligonucleotide probes.

Sapolsky et al. generally describes the use of arrays that discriminate against three genotypes for a given marker, e.g., the heterozygote or either of the two homozygotes (See description on Page 1). The arrays have first and second groups of probes that are complementary to first and second variants of the target nucleic acid sequence, respectively. The

arrays also have third and fourth groups of probes having a sequence identical to the first and second groups, respectively, but including all possible monosubstitutions of positions in the sequence that are within "n" bases of a base corresponding to the polymorphism, where "n" is from 0 to 5 (Summary of the Invention, page 2). This strategy is employed to screen for "useful markers for genetic linkage analysis" (See page 4, lines 30-39). However, nowhere does Sapolsky et al. teach or suggest an array comprising oligonucleotides comprising a plurality of HLA Class I oligonucleotide probes.

To establish a prima facie case of obviousness, three requirements must be satisfied. First, the prior art reference or combination of references must teach or suggest all of the limitations of the claims. *See In re Wilson* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art"). The teachings must come from the prior art, not from Applicants' disclosure. *See In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Second, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. *In re Oetiker,* 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Third, the proposed modification or combination of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

Applicants claim a microarray comprising a plurality of HLA Class I oligonucleotide probes on a solid support, wherein said plurality of probes comprises at least 80% of polymorphisms in the HLA Class I locus. Neither Betinotti et al. nor Sapolsky et al. teaches or suggests a plurality of oligonucleotide probes comprising at least 80% of polymorphisms in the HLA Class I locus. Betinotti et al. discusses HLA Class I polymorphisms, but detects these polymorphisms by sequencing PCR products, not with the use of probes designed to hybridize to those polymorphisms. Sapolsky et al. teaches of microarrays comprising oligonucleotide probes, but does not teach or suggest a plurality of oligonucleotide probes comprising at least 80% of polymorphisms in the HLA Class I locus. Furthermore, there is no suggestion or motivation

found either of these references to modify the sequence information of Betinotti into oligonucleotide probes for use in the arrays of Sapolsky.

Because all of the limitations of claims 1-3 cannot be found in the combination of Betinotti et al. and Sapolsky et al., and further, there is no motivation found to modify the teachings of one reference based upon the other in order to produce the claimed invention, claims 1-8 are not obvious over Betinotti et al. in view of Sapolsky et al. Accordingly, Applicants respectfully request that this rejection be withdrawn.

B. Claim 9 stands rejected over Bettinotti et al. (1997) in view of European Patent No. EP0785280 to Sapolsky et al. (1997), and further in view of U.S. Patent No. 5,412,087 to McGall et al. Applicants' claim 9 recites a microarray wherein the solid support is a glass slide.

It is stated in the Office Action on Page 8 that McGall et al. teaches spatially-addressable immobilization of oligonucleotides to create arrays using photolithographic techniques, and specifically teaches arrays wherein the solid support is a glass slide.

However, for at least the reasons stated above, claims 1-8 are not obvious over Betinnotti et al. in view of Sapolsky et al., and the elements and suggestions missing from these references are not provided by McGall et al. Claim 9 depends from and incorporates all the limitation of claim 4, which in turn depends from and incorporates all the limitations of claim 1, which recites a plurality of oligonucleotide probes comprising at least 80% of polymorphisms in the HLA Class I locus. None of these references teaches or suggests this claim limitation.

Accordingly, it is respectfully requested that this rejection of claim 9 be withdrawn.

C. Claims 10 and 11 stand rejected under 35 U.S.C. § 103(a) over Bettinotti et al. (1997) in view of European Patent No. EP0785280 to Sapolsky et al. (1997), and further in view of U.S. Patent No. 5,556,752 to Lockhart et al.

Claim 10 recites that the oligonucleotide probes are present on the solid support at a surface density of from about 250 to about 450 angstrom^2/molecule. Claim 11 recites that the oligonucleotide probes are present on the solid support at a surface density of from about 325 to about 375 angstrom^2/molecule. It is alleged in the Office Action that the description in Lockhart et al. of oligonucleotides found on an array that are approximately 100 angstroms apart is

necessarily the same as the surface density ranges recited in claims 10 and 11. Applicants respectfully disagree.

First, for the reasons stated above, claims 1-8 are not obvious over Betinnotti et al. in view of Sapolsky et al., and the elements and suggestions missing from these references are not provided by Lockhart et al. Claims 10 and 11 depend from and incorporate all the limitation of claim 4, which in turn depends from and incorporates all the limitations of claim 1, which recites a plurality of oligonucleotide probes comprising at least 80% of polymorphisms in the HLA Class I locus. None of these references teach or suggest this claim limitation.

Second, the Examiner has not shown how the array of Lockhart et al., with "an average spacing of approximately 100 angstroms," teaches the recited density limitations of Applicants' claims 10 and 11.

Third, the type of array found in Lockhart et al. is qualitatively different from the array examples disclosed by Applicants' specification. The array of Lockhart et al. consists of "unimolecular, double-stranded oligonucleotides on a sold support" (column 21, lines 8-11; Figures 1a-1f). The exemplary array comprises 16 separate, unimolecular DNA molecules formed onto the surface of the array (column 21, lines 33-50). Each single molecule had an average spacing of approximately 100 angstroms (column 22, lines 54-59).

The probes of the present invention are not intended to participate in the formation of a duplex as found in Lockhart et al., where the outer strand of one molecule formed a double-stranded structure with the outer strand of a neighboring molecule. The probes of Applicants' invention are not intended to form a double-stranded molecule with itself or with a neighboring probe molecule. The probes are instead intended to complex with the sample labeled DNA. Therefore, one skilled in the art would have no motivation to provide an array with the spacing found in Lockhart et al. for the purposes served by Applicants' invention.

Accordingly, claims 10 and 11 are not obvious over Bettinotti et al. in view of Sapolsky et al., and further in view of Lockhart et al., and Applicants respectfully request that this rejection be withdrawn.

V. New Claims 21-50

New claims 21-50 are also novel and non-obvious for the reasons stated above. Independent claim 25 is directed to an array comprising locus polymorphisms of the HLA Class I region. Independent claim 38 is directed to an array comprising a plurality of oligonucleotides, said plurality consisting essentially of oligonucleotides comprising locus polymorphisms of the HLA Class I region. Applicants respectfully submit that none of the references discussed above teaches or suggests these claim limitations.

VI. Conclusion

In light of the foregoing, Applicants respectfully assert that this application is in condition for allowance, which action is respectfully requested.

Respectfully submitted,

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